

CYP3A5

Genetic polymorphism in HIV-patients.



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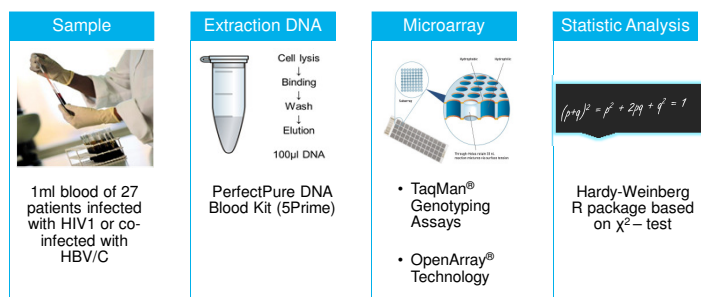
Review

A number of relevant polymorphisms are known for affecting the most common prescribed ARVs (antiretroviral), inducing drug toxicity, risk of virologic failure and may explain the interpatient variability for drug absorption pathways. CYP3A5 is an isoform of Cytochromes P450A family, estimated to participate in the metabolism of 40 to 60% of all clinically administered drugs, namely atazanavir (1). The aim of this study was to characterize the CYP3A5 polymorphisms of HIV-infected patients, from Santa Maria Hospital, Lisbon, Portugal.

Objectives

The aim of this study was to characterize the Cyp3A5 polymorphisms of HIV-infected patients, from Santa Maria Hospital, Lisbon, Portugal.

Experimental Methods



Population Characteristics

Is composed of 367 individuals infected with HIV-1 receiving ARV therapy. In terms of gender, 253 are male and 114 are female. In relation to the race are 275 Caucasian, 114 African and 38 unknown.

Single-Nucleotide Polymorphism Analysis

2 SNP (single nucleotide polymorphism) with pharmacogenetics relevance, located at CYP3A5 gene, were genotyped by Microarray analysis: CYP3A5, A6986G, rs776746 and CYP3A5, 27131_27132, inst rs71303343.

SNP ID	Gene	Assay ID	Alleles tested	n Samples tested
rs776746	CYP3A5	C_26201809_30	C/T	332
rs41303343	CYP3A5	C_32287188_10	A/DEL	348

Conclusion

With the profile obtained by genetic characterization, performed in this study, we can conclude that the genotype frequencies for both SNP are not the same among the groups caucasian and african.

CYP3A5*3 (rs776746) is the most common non-functional allele of the gene (2), and seems to be an import contributor to individual and inter rational variation in CYP3A5 mediated metabolism of drugs. The CYP3A5*3 (rs776746) results evidenced more heterogeneity in the population,, according to the literature.

Our study revealed a significant frequency of risk alleles, CYP3A5*3 and CYP3A5*7, associated with drug efficacy, safety and recommend dosage. Therefore, could provide clinical useful information on ARV in HIV Portuguese population.

References

- Population differences in major functional polymorphisms of pharmacokinetics/pharmacodynamics-related genes in Eastern Asians and Europeans: implications in the clinical trials for novel drug development. Kurose K, Sugiyama E, Saito Y. . Drug Metab Pharmacokinet. 2011
- Pharmacogenetics of antiretroviral therapy. Barreiro P. Expert Opinion on Drug Metabolism & Toxicology. Pags 1119-1130 Volume 10, Issue 8, 2014

Results

- The SNP Hardy-Weinberg equilibrium (HWE) (p-value ≥ 0.05): rs776746 and rs41303343 p-value <0.0001 , (table 1).
- Allelic frequencies for mutated alleles were: rs776746 82.6% and rs41303343 1.96%, (table1).
- Genotype frequencies by gender and per race were statically significant (p-value ≥ 0.05), (table 2 and 3).

Table1 Genotype and allele frequencies of the analysed polymorphisms

Gene/SNP ID	N	Genotype	n	Freq.(%)	95% CI	P-value
CYP3A5	332	-/-	321	96.69	(94,98.3)	$<0.0001^*$ (cc)
		-/T	9	2.71	(1.3,5.3)	
		T/T	2	0.60	(0.1,2.4)	
		-	651	98.04	(96.6,98.9)	
CYP3A5	354	T	13	1.96	(1.1,3.4)	$<0.0001^*$
		AA	28	7.91	(5.4,11.4)	
		AG	67	18.93	(15.1,23.5)	
		GG	259	73.16	(68.2,77.7)	
		A	123	17.37	(14.7,20.4)	
rs776746		G	585	82.63	(79.6,85.3)	

cc -- Continuity correction; * significant at 5% level

Table2 Allele and genotype frequencies and percentage per race for CYP3A5

Gene/SNP ID	Allele	Caucasian (%)	Negroid (%)	P-value
CYP3A5	-	458 83.58	78 14.23	<0.0001 (a)*
rs41303343	T	2 0.36	10 1.82	
CYP3A5	A	41 7.04	62 10.65	0*
rs776746	G	449 77.15	30 5.15	

(a) p-value computed via monte carlo simulation; * significant at 5% level

Table 3: Frequencies and percentage per gender for CYP3A5

Gene/SNP	Genotype/Alele	Male (%)	Female (%)	P-value
CYP3A5	-/-	206 67.1	91 29.64	0.233 (a)
rs41303343	-/T	3 0.98	5 1.63	
	T/T	1 0.33	1 0.33	
CYP3A5	-	415 67.6	187 30.5	0.059
	T	5 0.8	7 1.1	
	AA	10 3.08	14 4.31	
rs776746	AG	47 14.46	15 4.62	0.007
	GG	168 51.69	71 21.85	
	A	67	43	
	G	383	157	0.049*

(a) p-value computed via monte carlo simulation; * significant at 5% level

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